Psoriasis: implications of biologics
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Citation for published version (APA):

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General introduction and aims of the thesis
Introduction

Although sometimes mixed up with for example leprosy in early times, psoriasis is viewed as a separate entity since 1841.\(^1\) It is a common chronic dermatological entity that affects probably 2% of the population. Epidemiological studies from around the world have estimated the prevalence of psoriasis to be 0.6 to 4.8%.\(^2\) The variation in these percentages can be explained by study methods, e.g. the definition of prevalence, the case definition of psoriasis, the population and ages studied, and their sampling techniques.\(^2\) Furthermore, prevalence of psoriasis is known to vary among different populations. This might perhaps be explained by differing evolutionary pressure of epidemic infections, which has led to genetic changes.\(^3\)

A genetic component in the development of psoriasis is suggested by the fact that about 30% of psoriasis patients have an affected first degree relative.\(^4\) Twin studies confirm this by showing a 67% concordance for monozygotic twins versus 18% for dizygotic twins.\(^5\) Most investigators consider psoriasis a multifactorial disease in which several genes interact with each other and with environmental stimuli.\(^6\) At least nine chromosomal loci have been identified that are evidently linked to psoriasis.\(^4\) However, the exact genes and their functions playing a role in psoriasis have not yet been unambiguously identified.\(^3\)

Psoriasis affects people of all ages, and its incidence peaks in early adult life (20s) and then again in later adult life (50s and 60s).\(^7\) Sharply demarcated erythematous lesions are the most important features of the disease. These lesions can vary from very small to very large plaques. Furthermore, several separate psoriatic entities exist, such as guttate psoriasis (small drop-shaped lesions), erythrodermic psoriasis (covering almost the complete body) and pustular psoriasis (with clinically recognizable pustules).\(^1\) This thesis focuses on chronic moderate to severe plaque type psoriasis, in which coin-sized or palm sized plaques predominate. This phenotype accounts for 90% of all psoriasis cases.\(^4\) Additionally, between 5 and 42% of patients with psoriasis have psoriatic arthritis, a destructive and occasionally disabling joint disease.\(^6\)

Although psoriasis is primarily a dermatological condition, it affects more than skin alone. Research shows that psoriasis predisposes patients for other conditions. Neimann et al. found that diabetes, hypertension, hyperlipidemia, smoking, and increased Body Mass Index (BMI) are associated with both mild and severe psoriasis.\(^7\) Also when controlled for cardiovascular risk factors, psoriasis appears to be an independent risk for myocardial
infarction, mainly in young patients with severe psoriasis. Furthermore, the prevalence of arthritis, depression, suicidal ideation, inflammatory bowel disease and lymphoma appears higher in psoriasis patients compared with the general population. Recently an association between psoriasis and increased mortality was found. According to a population based study, male and female patients with severe psoriasis die an average 3.5 and 4.4 years younger, respectively, than patients without psoriasis.

Additionally, much attention has been given to the impact of psoriasis on quality of life (QoL) in the last decade. Health related quality of life (HRQoL) is markedly reduced in patients with psoriasis, and psoriasis impacts all dimensions of HRQoL. Rapp et al. compared HRQoL scores of psoriasis patients with other chronic diseases like cancer, type II diabetes, chronic lung disease, hypertension, myocardial infarction, depression, congestive heart failure and arthritis. The means for patients with psoriasis for both physical functioning and mental functioning were among the lowest of all the groups. This comparison implies that, though not threatening to life itself, psoriasis can severely threaten the quality of life. This impact is probably mediated by the mental or physical difficulties patients have to deal with during the course of the disease and the various treatment regimens. Patients with psoriasis report physical discomfort, impaired emotional functioning, a negative body and self-image, and limitations in daily activities, social contacts, activities and work. In addition, psoriatic patients often suffer from experiences of stigmatization related to the disease in higher levels of stigmatization than do other dermatological patients. Feelings of stigmatization are especially elicited by experiences of rejection. Patients with skin disorders often experience social rejection when people avoid touching them, possibly fearing contagion or filth. Psoriasis patients may feel humiliated when they need to expose their bodies during intimate relationships, swimming in public places, using public showers, or living in conditions that do not give appropriate privacy.

It is not established whether the increased prevalence of diabetes, hypertension, hyperlipidemia, smoking, increased BMI, and myocardial infarction is independent (although these factors are interrelated) or that it is the result of the decrease in QoL and the treatments that psoriasis patients undergo.
**PATHOGENESIS AND DEVELOPMENT OF THERAPIES**

Theories on the pathophysiology of psoriasis have changed over the years and greatly influenced the development of the treatment armamentarium. However, the first effective therapies were developed through an empirical approach not based on hypotheses of disease pathogenesis or properties of the therapeutics. Phototherapies were already introduced in 1925 when a combination of topical crude coal tar and subsequent UV irradiation was applied. This treatment became a standard therapy for psoriasis for half a century, particularly in the USA. In the 1970s it was shown that broadband UVB radiation alone, if given in doses that produce a faint erythematous reaction, could clear the milder clinical forms of psoriasis. In 1974 it appeared that the combination of orally administered 8-methoxypsoralen (8-MOP) and subsequent exposure to a new high intensity UVA radiation source was a highly effective treatment for psoriasis. This new therapeutic concept was termed photochemotherapy or PUVA. Until then, research into the aetiology of psoriasis concentrated on abnormalities in keratinocyte differentiation and proliferation. Psoriasis was considered mainly a disorder of epidermal hyperproliferation, decreased epidermal turnover time (i.e. accelerated cell cycle kinetics), with resulting abnormal terminal differentiation and associated impaired barrier function of the epidermis. This was due to the clinical and histological appearance of the disease including thick, scaling plaques and epidermal hyperplasia, parakeratosis, and absence of a granular layer, respectively. The proliferative cell population is approximately doubled in psoriasis, whereas the cell cycle is more than 8 times shorter (36 vs. 311 hours) and daily production of keratinocytes in psoriatic lesions is approximately 28 times greater than that in normal epidermis. The cause for such multiplication of cells was not elucidated. This initial view of psoriasis as an epidermal disease resulted in the use of therapeutic approaches that used antimetabolites such as methotrexate or arsenic to counteract the epidermal hyperproliferation. The assumption that methotrexate specifically targeted keratinocyte hyperplasia led to the development of other epithelial-targeted therapeutics like synthetic retinoids and vitamin-D derivates. Accidentally, it was observed that psoriatic patients who had received solid organ transplants and were treated with cyclosporine to prevent rejection, showed significant improvement in their psoriasis. The discovery that immunosuppressive agents improved psoriasis, changed the beliefs about the pathogenesis of the disease. Around 1979 it was shown that epidermal changes in psoriasis were preceded by dermal infiltrates consisting of T-cells and macrophages. More evidence pointed towards T-cells, like the experience of patients who received bone marrow transplants from psoriatic donors and then developed psoriasis themselves. The success
of a fusion protein consisting of interleukine-2 (IL-2) and diphtheria toxin that specifically targeted T-cells and not keratinocytes, gave T-cells a definitive role in the pathogenesis of psoriasis.6,18 Our department was the first to propose a potential role of the cellular immune system in disease pathogenesis. Marked infiltration of psoriatic lesions by T-cells was shown by applying monoclonal antibodies for the immunohistochemical detection of leukocyte subsets.21 In the same period many other immune-related molecules were discovered and it was shown that T-cells in psoriasis were mainly activated memory T-cells. The T-cell differentiation was found to be strongly polarized towards the type 1 pathway, associated with the production of interferon-γ (INF-γ) and tumour necrosis factor α (TNF-α).16 All together the view was adopted that an activated cellular immune system was a common feature of psoriatic lesions and that inappropriate immune activation may be pathogenic.16

IMMUNOPATHOGENESIS
The immune system uses two major effector pathways to defend the host: innate and adaptive immune responses. Both pathways contribute to the pathophysiology of psoriasis. The innate immunity is designed to respond rapidly against danger, such as invading microbes, but has a limited repertoire and does not develop a long lasting memory. Adaptive immunity that develops within a few days after the first exposure to a pathogen is antigen-specific and can respond to a wide range of different antigens. The latter develops an immunological memory resulting in a pool of memory lymphocytes that can easily be activated.19 Nowadays, the innate immunity may be considered to be the main culprit in the pathogenesis of psoriasis, although for many years this role was assigned to the adaptive immunity.22 Practically all cellular and humoral elements of the innate part of the skin immune system in psoriasis are up-regulated or increased in lesional skin of psoriasis patients.3 Surprisingly, the leading part in this theory is for T cells, though a specific type of T cells: T cells expressing natural killer receptors belonging to the innate immunity and producing IFN-γ. These lymphocytes express natural killer receptors (NKR)s and T-cell receptors (TCRs) and they may represent the link between the innate and adaptive immunity in psoriasis.23 It is thought that natural killer T cells, dendritic cells, neutrophils and keratinocytes respond in an exaggerated way to an unknown trigger. They produce pro-inflammatory cytokines, TNF-α being among the most important ones. TNF-α is increased in lesional skin of psoriasis patients and is able to induce a cascade of other cytokines including IL-1, IL-1RA, IL-2, IL-4, IL-6, IL-10, IL-12, IL-18 and IFN-γ. This subsequently leads to recruitment and activation of preferentially type 1 T cells.24
Th17 lymphocytes and psoriasis: cellular and molecular interactions with skin-resident cells. In the 'IL-23/Th17 axis' model for psoriasis, Th17 lymphocytes (Th17) interact with skin-resident cells, contributing to the psoriatic phenotype. In the dermis, IL-23, secreted by dermal dendritic cells (DDC), is able to induce Th17 lymphocyte activation with the consequent release of proinflammatory cytokines, such as IL-17A, IL-17F, IL-22, and IL-26. IL-17A, IL-17F, and IL-22 act on keratinocytes (KC) leading to epidermal hyperplasia, acanthosis, and hyperparakeratosis. Dermal CCR5\(^\text{+}\)CXCR3\(^\text{+}\)CXCR6\(^\text{+}\) Th1 and epidermal VLA-1\(^\text{+}\) Tc1 lymphocytes are activated by DDCs and produce TNF-\(\alpha\) and IFN-\(\gamma\), contributing to the pathogenesis of the disease. KC hyperproliferation might also be influenced by fibroblasts, which can release keratinocyte growth factor (KGF) through TNF-\(\alpha\) stimulation. In the context of this proinflammatory milieu, activated KCs might produce IL-23, which could mediate a cross-talk with Th17 lymphocytes in synergy with IL-23 coming from DDC. Th17 cells induce KC to produce IL-8 and antimicrobial peptides (for example, S100A8, S100A9, and defensin b1/2) for recruitment of neutrophils, cathelicidin for activation of plasmacytoid dendritic cells (PDC), and vascular endothelial growth factor (VEGF) with resulting angiogenesis.

In addition to the TH1 cells, the infiltrate in the lesional psoriatic skin also contains TH17 cells (key cytokines IL-17 and IL-22). The presence of TH17 cells is consistent with the described role of this cell type in a variety of chronic inflammatory autoimmune-type diseases. There is growing evidence supporting a major role of TH17 cells and TH17-related cytokines, like IL-17 in psoriasis (see figure 1). The first observation that IL-17 could be a relevant cytokine in psoriasis was found in the late 1990s by Teunissen et al. They found detectable levels of IL-17 mRNA in lesional psoriatic skin, but not in non-lesional skin. The majority of the CD4+ and CD8+ T cell clones derived from lesional psoriatic skin expressed IL-17 mRNA, suggesting that skin-infiltrating T cells can produce this cytokine, which by itself stimulates inflammatory cytokine production in keratinocytes. TH17 cells also produce IL-22, which strongly stimulates keratinocyte proliferation and may be responsible for acanthosis (epidermal thickening), a typical feature of psoriasis. In addition to T cells, a special subset of myeloid dendritic cells in the skin has also been implicated in the pathogenesis of psoriasis. These dendritic cells are characterized by high production of TNF-α and TH1 and TH17 cell-polarizing properties. The activated TH1 and TH17 lymphocytes and dendritic cells amplify the inflammatory reaction by releasing a series of cytokines with chemotactic and activating functions towards neutrophils, monocytes and keratinocytes. This leads to keratinocyte proliferation, angiogenesis, leukocyte immigration, finally resulting in chronic psoriatic plaques.

**CURRENT TREATMENT**

All previously mentioned immunological changes on the cellular level result in the psoriatic phenotype. Clinical manifestations of psoriasis are heterogeneous, ranging from limited disease to very extensive disease. The majority of patients (approximately 80%) have limited disease, whereas approximately 20% of patients have more extensive skin involvement.

Most patients with limited disease are treated in the first line. In a large UK prevalence study, using the General Practice Research Database, it was shown that topical corticosteroids were the most frequently prescribed medications, used by 61.4% of patients. The next most commonly used therapies were corticosteroid combination products (40.4% of patients), topical vitamin D analogues (39.0% of patients), and topical tar (24.5% of patients). Systemic agents were used by 2.3% of patients.

Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. They are available in many strengths and formulations, which allows for
versatility of use. The mechanisms of action of corticosteroids include anti-inflammatory, antiproliferative, immunosuppressive and vasoconstrictive effects. Another common topical therapy is synthetic vitamin D analogues, like calcipotriol. The mechanism of action of the vitamin D analogues in psoriasis is believed to be mediated by their binding to vitamin D receptors, which leads to both the inhibition of keratinocyte proliferation and the enhancement of keratinocyte differentiation.

Additional topical therapies are dithranol, tazarotene, calcineurin inhibitors, tar and combination treatments. It is generally accepted that topical treatments are inadequate as soon as psoriasis reaches 10–15% of the body surface. Broad band ultraviolet radiation in the waveband 290-320 nm (UVB), or narrow band UVB 311 nm are an effective treatment of guttate or plaque psoriasis resistant to topical therapy. Patient compliance is usually good, with the treatment viewed as an escape from the problems of topical agents. Restrictions in use for individual patients often relate to time off work and travel costs.

Another form of phototherapy is oral or topical psoralens followed by irradiation with long wave ultraviolet (320 to 400 nm, UVA). Topical psoralens may be applied by taking a bath to which it has been added. This is an established, effective, widely used form of treatment (Psoralens + UVA = PUVA). Acute adverse effects consist of skin burning, nausea and pain, whereas chronic consequences consist of skin ageing, pigmentation and carcinogenicity. Nevertheless, PUVA is used for more difficult to clear psoriasis resistant to topical preparations and UVB.

Next step in the psoriasis treatment armamentarium are the conventional systemic therapies. Approved for chronic plaque psoriasis are cyclosporine, methotrexate, and acitretin. Fumaric acid esters are registered in Germany and used off-label in some other countries. Although effective for many patients, use of these traditional systemic therapies is often limited by toxicity. In a systematic review on systemic therapies for psoriasis, withdrawals were highest for fumaric acid esters and methotrexate resulting mostly from gastrointestinal and hepatic adverse events respectively.

**IMMUNOLOGICAL BASED THERAPIES**

For a proportion of patients, the available psoriasis therapies, including topical treatments, phototherapy and the conventional systemic treatments are not sufficient. They may lack effectiveness, are inconvenient, not tolerated or contra-indicated. The increasing knowledge on the pathogenesis of psoriasis has led to the development of more specific
immunomodulating therapies: ‘biologic response modifiers’ or ‘biologics’. These agents are custom-made, protein-like molecules constructed to specifically target a particular cell type or cytokine involved in the pathogenesis of psoriasis.34 Since 1989 a range of biological therapies have been tested for psoriasis. Among these first biologics for psoriasis were the T-cell targeted therapies like the murine anti-CD4 and anti-CD-3 antibodies, followed by humanized anti-CD2, anti-CD25, anti-CD80 and anti-CD11a.35-40

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Table 1. EMEA and FDA registration dates for the biologics for psoriasis

Alefacept (Amevive®), anti-CD2, was the first biologic to be approved by the FDA in the USA in January 2003 for psoriasis only (see table 1). The EMEA, however, requested more clinical information for the approval of alefacept for psoriasis in Europe. Biogen withdrew its application and planned to develop the additional clinical information necessary before refiling, which it predicted could take several years.41 The only European country in which alefacept is used is Switzerland. Alefacept is an intravenously or intramuscularly administered fusion protein combining a portion of human immunoglobulin (IgG) and the binding site of lymphocyte function-associated antigen-3 (LFA-3). It binds to CD-2, the partner molecule of LFA-3 located on the surface of T cells resulting in inhibition and memory T cell activation and proliferation.34 With alefacept two randomized, double-blind, placebo-controlled registration studies were done in which 28 to 40% of the patients achieved 75% improvement in PASI (PASI-75) after 12 weeks.42-43 There have been no head-to-head studies of alefacept versus other biological or conventional drugs. Safety warnings in the drug label consider the risk of lymphopenia, malignancies, serious infections and precautions for allergic reactions.32

Efalizumab (Raptiva®) was the first biologic to be registered for plaque psoriasis in Europe and the USA and was not registered for another indication. Efalizumab binds
to CD11a which is a subunit of leukocyte function-antigen-1 (LFA-1) that is expressed on all leukocytes. For adherence of leukocytes to other cell types, it is necessary that CD11a binds to intercellular adhesion molecule-1 (ICAM-1). By binding of efalizumab to CD11-a, the binding of ICAM-I to LFA-1 is not possible; this interrupts many processes including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells and migration of T lymphocytes to sites of inflammation including psoriatic skin. In clinical registration studies, 22-39% of patients achieved PASI-75 after 12 weeks with 1 mg kg⁻¹/wk efalizumab. Safety warnings in the drug label consider the risk of serious infections, malignancies, immune-mediated trombocytopenia, immune-mediated hemolytic anaemia and psoriasis worsening (as well as variants). Precautions are mentioned for arthritis events, immunosuppression, immunizations and first dose reactions. In February 2009 the European Medicines Agency (EMEA) has recommended the suspension of the marketing authorization for efalizumab. The EMEA’s Committee for Medicinal Products for Human Use (CHMP) had concluded that the benefits of efalizumab no longer outweigh its risks, because of safety concerns, including the occurrence of progressive multifocal leukoencephalopathy (PML) in three patients taking the medicine. In reaction, Merck Serono has voluntarily withdrawn efalizumab from the market worldwide. In the following months all patients using efalizumab have been changed to another suitable medication. At this moment it is unknown whether efalizumab will ever re-enter the market for psoriasis or for another indication.

Registration for etanercept followed soon after registration of efalizumab in both Europe and the USA. Etanercept (Enbrel®) is administered subcutaneously and was the first TNF-α inhibitor approved for psoriasis. At this moment etanercept is indicated for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and paediatric plaque psoriasis. It is a TNF-α receptor antagonist which is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. Etanercept inhibits binding of both TNF-α to cell surface TNF-α receptors, rendering TNF-α biologically inactive. As a result, etanercept can also modulate biological responses that are induced or regulated by TNF-α, including serum levels of cytokines, expression of adhesion molecules responsible for leukocyte migration and to a lesser extent intercellular adhesion molecule-1 (ICAM-1). In clinical trials, after 12 weeks of treatment PASI-75 response rates of low dose etanercept (25 mg twice weekly) and high-dose etanercept (50 mg twice weekly) were 30–34% and 47–54% respectively. Safety warnings in the drug label consider the risk of infections.
Infliximab (Remicade®) is a chimeric monoclonal antibody working against TNF-α. It is composed of human constant and murine variable regions. Infliximab binds specifically to human TNF-α and is administered intravenously once every two months after a loading period. Apart from plaque psoriasis, it is also indicated for psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn’s disease and paediatric Crohn’s disease. Due to the rapid action of infliximab it is also used as rescue treatment for psoriasis exacerbations. Continuous treatment with infliximab 5 mg/kg at weeks 0, 2, 6, and every 8th week thereafter resulted in PASI-75 response rates of 78–82% after 24 weeks and 55–61% after 1 year. The administration of infliximab may be complicated by infusion reactions that may limit its use. Safety warnings in the drug label consider the risk of serious infections and hepatosplenic T-cell lymphomas.

Another monoclonal antibody that inhibits TNF-α is adalimumab (Humira®). Differences between infliximab and adalimumab are that adalimumab is completely human and is administered subcutaneously once every two weeks. Adalimumab has only recently been registered for psoriasis in Europe and the USA, although introduced for rheumatoid arthritis already in 2003. Other indications for adalimumab are Crohn’s disease, ankylosing spondylitis, psoriatic arthritis and polyarticular juvenile idiopathic arthritis. In the meta-analysis of efficacy of systemic treatments for moderate to severe psoriasis, only one study with adalimumab was included. In this study PASI-75 response rates were reported of 71% after 16 weeks and 70% after 24 weeks of treatment. Also for adalimumab safety warnings in the drug label consider the risk of serious infections.

Ustekinumab (Stelara®) is the most recent registered biological therapy for psoriasis, not yet routinely used in most countries. It is the first IL-12/23 inhibitor approved although a second one is in the pre-registration phase, ABT-874. IL-12 and IL-23 share the same subunit, p40, which is considered to play a substantial role in the pathogenesis of psoriasis. The proportion of patients in a large clinical phase III trial who had a PASI-75 response after 12 weeks varied between 66.7% and 75.5% depending on the dose. Remarkable is the low dosing frequency, at week 12 patients have only had two administrations of the drug. Although the median half-life (t1/2) of ustekinumab is approximately 3 weeks, the dosing frequency is once every three months. This might seem a major advantage, but the treatment can not be ceased in case of an infection or non-elective surgery.
CLINICAL CHOICES

Spontaneous remission is suggested to occur in about a third of psoriasis patients. For all other patients, psoriasis is (still) an incurable chronic disease with periods of exacerbations, remissions and recurrences. As a result, most patients need lifelong therapy. Nowadays the historical view of treatment only to reduce symptom severity or reverse disease progression has changed to a more comprehensive view that effective treatment should also improve the patient’s functional level and overall well-being. Therefore, treatment should be tailored to meet individual patients’ needs. These needs vary depending on body location, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. Regarding choice of therapy, it is important to match patient expectations with practical considerations. Patients who wish for lifetime clearance with no evident lesions will inevitably be disappointed. For instance, when using topical therapy a continuous intense topical regimen would be needed that will be very difficult to carry out and maintain. Other patients may prefer only intermittent treatment with little interest in spending considerable time to care for their psoriasis.

A survey study on compliance with treatment has been done in 120 psoriasis patients of whom 55% was using topical treatments, 10% systemic treatments, 2% phototherapy and 30% was using a combination of treatments. Sixty-one percent of the population sampled reported that they always complied with treatment regimens prescribed by their dermatologist, whereas 39% said that they “sometimes” or “never” complied. When a treatment is started, the efficacy should be evaluated after an appropriate period to prevent loss of compliance and undertreatment in case of unsatisfactory results. It is important to ascertain each patient’s goals and then develop a strategy to help fulfil his or her expectations while also being practical and realistic. The pros and cons of alternatives should be balanced against each other: is there choice between a painful injection and a pill? Is the frequency of one drug once weekly and the other a daily reminder of the patients’ disease? On the other hand, treatment with a two or three month’s interval may seem preferable for the patient, but in case of a complication the treatment cannot be intervened. In a survey of patients with psoriasis as to the desired treatment benefit, the following criteria were named most often: healing of all skin lesions, reduction of pruritus and burning on the skin, less loss of time devoted to treatment, healing of all exposed lesions, avoidance of strong side effects of treatment and fewer visits to physician or clinic. Several guidelines are available that advise on treatment algorithms and a common European guideline on psoriasis therapies is in progress. Nevertheless, the
existing guidelines do not take into consideration the patients preferences and satisfaction with psoriasis therapies.

Another factor that should be taken into account when clinical choices are made, are the costs. Since psoriasis is a chronic disease, clinical choices may have great impact on the health care costs of the patients. Topical therapies and the conventional systemic treatments in general are not expensive in contrast to phototherapy, hospitalization and the biologics.

These high costs are a factor withholding widespread use of the biologics for psoriasis, the average medication costs for a biologic per year are € 12 000. In case of non-optimal response, in some of the biologics the dose may be doubled with costs rising accordingly. However, an alternative would be switching to another biologic which would save an extra € 12 000 a year in that situation. Considering the burden of the biologics on the health care budget, in many countries reimbursement criteria are applied. These criteria may demand failure of or intolerance to conventional systemic therapies before biologics can be prescribed. Nevertheless, since the introduction of the biologics, the number of patients hospitalized for psoriasis has dropped dramatically to a decrease of 90% (unpublished data), which partly compensates the costs of the biologics.

Last but not least, safety is an important issue when clinical choices are made. Especially for psoriasis patients, since most patients need lifelong therapy.

Short term data from phase III trials show pooled monthly adverse events incidence rates of 28.3% for efalizumab, 17.8% for infliximab, 17.6% for etanercept and 16.6% for adalimumab. Common adverse events for infliximab are infusion reactions consisting mainly of chills, headache, flushing, nausea, dyspnoea, injection site infiltrations, and taste perversion. Most of these reactions are mild or moderate in severity. Other adverse events that were reported most often in infliximab trials were headache, fatigue and upper respiratory tract infections. For etanercept the most common adverse events are also headache, fatigue and upper respiratory tract infections. Furthermore, injection site reactions occur very often, which are usually mild. For adalimumab upper respiratory tract infections, nasopharyngitis and headache were reported most often. Apart from the events resulting from mode of administration, there is great resemblance of the most common adverse events for these three biologics, which suggests a direct result of their pharmacological action inhibiting TNF-α. For efalizumab the most common adverse events were headache, chills, nausea, infection (not defined), myalgia and pain.
Since the biologics have only been used several years for treatment of psoriasis patients at this moment, many long-term issues regarding their safety profiles are not sorted out yet. Of the conventional psoriasis therapies long-term risks are evident and applicable safety measures can be taken. Methotrexate for instance has a track record of over 40 years in psoriasis therapy which has led to treatment guidelines involving liver biopsies (now mostly replaced by the amino terminal type III procollagen peptide (P3NP) assay), specific laboratory checks and the use of test doses. Another example is the prescription of topical corticosteroids in pulse schemes, which prevents the occurrence of skin atrophy as side effect. PUVA therapy has most extensively been investigated by means of a 30-year follow-up study. This led to the finding that about 15 years after the first treatment with PUVA, the risk of malignant melanoma increases.63 This is a clear example of the need for long-term follow-up for safety issues.

For all the biologics long-term data are especially necessary to confirm or reject the possible increased risk of malignancies and to identify rare adverse events, like PML was found in the case of efalizumab. For rheumatologic patients there is evidence of an increased risk of serious infections and a dose-dependent increased risk of malignancies treated with TNF-α inhibitors.64 Since rheumatologists are years ahead with the use of biologics, we should benefit from their experience. Nevertheless, the populations differ and we need to confirm their findings in psoriasis patients. Besides adverse events, factors like antibody formation may impair treatment outcome. In rheumatologic patients it has been demonstrated that antibodies are formed against some of the biologics and that these antibodies may impair effectiveness.65 For psoriasis patients, it is not clear to what extent these antibodies are formed and what their clinical consequences are. Another issue evolves when patients have started a biological treatment which is not tolerated or is not effective enough and returning to conventional therapies is no option. In rheumatologic patients switching between biologics has been proven successful, but for psoriasis patients this is not known yet.66-68

Most of these issues, long-term adverse events, antibody formation and switching, cannot be investigated in randomized controlled trials and therefore systematic reviews, cohort studies, case-control studies and case reports/case series are also needed for a full safety profile.69
AIMS OF THE THESIS
Following their introduction, the clinical effectiveness of the biologics for psoriasis and the sometimes miraculous results have been cheered extensively. Unfortunately, the additional occurrence of unwanted side effects is inevitable. This thesis considers the implications of the introduction of the biologics for psoriasis, focusing on safety issues, treatment optimization and clinical choices.

Clinicians are encouraged to use clinical guidelines that are developed to guide them to the most effective and safest systemic therapies for psoriasis. However, the patients’ opinion of these therapies has been neglected in guideline development. Chapter 2 is a systematic review that shows all evidence on the patients’ preferences and satisfaction with systemic therapies for psoriasis.

Infliximab has been proved to be a fast-acting effective biological treatment for psoriasis. However, treatment with infliximab can be hindered by infusion reactions. In Chapter 3 the types of infusion reactions that can occur during infliximab therapy are reviewed as well as factors influencing the occurrence of these reactions. A treatment plan is offered and clinical choices are discussed.

Etanercept is the most commonly prescribed biologic for psoriasis with many satisfied patients. However, a remarkable part of these patients develop dermatological adverse events. Chapter 4 is a systematic review providing an overview of all dermatological adverse events of etanercept described in the literature (including all study types, case reports and surveys) and presenting the available information on incidence, severity, course of the adverse events and practical considerations.

Since patients may develop allergic symptoms when treated with a biologic, ways are sought to confirm a possible allergy to these therapies. Chapter 5 is a comment on the use of patch tests to determine hypersensitivity to etanercept and infliximab.

Adalimumab has only recently been introduced for treatment of moderate to severe psoriasis and shows good results. However, a substantial part of the patients do not respond to treatment with adalimumab or lose their initial response. Antibodies to adalimumab have been found to be a cause for this ineffectiveness in patients treated
with adalimumab for other indications. In Chapter 6 a prospective observational study is presented that investigates the extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis.

At this moment biological therapies form the end of the treatment spectrum for psoriasis. When a biological treatment cannot be continued, usually alternatives are scarce. The only option left might be to switch to another biologic. Chapter 7 presents the results of patients in our biologic registry who switched between biologics for psoriasis.

To address epidemiological questions on psoriasis and to improve the knowledge on the safety of the biologics large long-term observational cohort studies are a necessity. Chapter 8 summarizes the current status of national registries on biological and other systemic therapies for psoriasis in Europe. Also, the international cooperation of these registries, named ‘Psonet’ is presented.

The claims of effectiveness of therapies are based on the results of clinical trials. To measure the effectiveness in these clinical trials and in daily practice, severity and outcome measures for psoriasis are used. Although important decisions are based on the use of these measures, their quality has not clearly been evaluated. Chapter 9 is a systematic review to identify all clinical psoriasis measures that are used in RCTs and a quantitative assessment of the most important clinical severity and outcome measures for psoriasis.

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